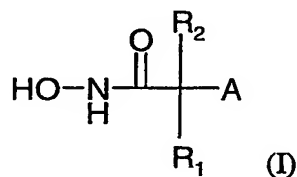


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Claims

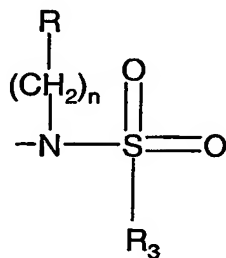
1. A method of treating cancer in a subject in need of such treatment which comprises radiotherapy, or cytotoxic therapy in combination with heat shock, and further comprises administering to the subject an effective amount of a matrix metalloproteinase.

2. A method of treating cancer in a subject in need of such treatment which comprises: radiotherapy, or cytotoxic therapy in combination with heat shock, and further comprises administering to the subject an effective amount of a matrix metalloproteinase inhibitor of the formula I



(i) wherein

A represents substituent of formula II or III;



Formula II

wherein

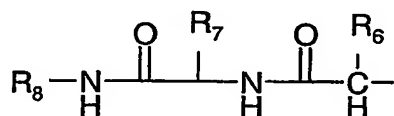
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R represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₃ represents aryl that may be unsubstituted or substituted by R₄ and R₅;

R₄ or R₅ represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluoromethyl or cyano, oxy-C2-C3-alkylene, 1- or 2-naphthyl; or R₄ and R₅ together on adjacent carbon atoms represent lower alkylenedioxy;

n represents an integer from 1 to 5;



Formula III

wherein

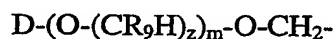
R₆ is C₃₋₁₂ alkyl, C₃₋₁₂ alkenyl, C₃₋₇(optionally hydroxy-, C₁₋₆ alkoxy-, amino-, or C₁₋₆ alkylamino- substituted) cycloalkyl, C₅₋₁₄ aryl, or C₅₋₁₄ aryl(C₁₋₆ alkyl), wherein aryl groups are optionally substituted by hydroxy-, C₁₋₆ alkyl-, C₁₋₆ alkoxy-, amino-, halo- or cyano-;

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R₇ is C₁₋₁₀ (optionally hydroxy- or C₁₋₆alkoxy- amino-, C₁₋₆ alkylamino-, thiol-, C₁₋₆ alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl, C₆₋₁₄ (optionally hydroxy-, C₆₋₁₄aryloxy-, or C₁₋₆alkoxy-, amino-, C₁₋₆ alkylamino-, halo-, or cyano-substituted)aryl, or indolylmethyl;

R₈ is methyl, pyridyl, or a substituent of formula X-Y- wherein X is morpholino, pyridyl or aryl, and Y is C₁₋₁₂alkylene in which up to four of the methylene (-CH₂-) units are optionally replaced with -CO-, -NH-, -SO₂- or -O-;

R₁ is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkyl-cycloalkyl, aryl-lower alkyl-lower cycloalkyl, lower alkyl-cycloalkyl, lower alkoxy-lower alkyl-cycloalkyl, aryl-cycloalkyl, cycloalkyl-lower alkyl-cycloalkyl, halo-lower alkyl-cycloalkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, N-lower alkylpiperidyl or a substituent of formula IV



Formula IV

wherein

z is 1, 2, 3 or 4;

m is 0, 1, 2 or 3;

each R₉ is

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independently H, C₁₋₁₀ (optionally hydroxy-, C₁₋₆ alkoxy-, amino-, C₁₋₆ alkylamino-, thiol-, C₁₋₆ alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, C₂₋₆ alkenyl, C₆₋₁₄(optionally hydroxy-, C₁₋₆ alkoxy-, amino-, C₁₋₆ alkylamino-, halo- or cyano-substituted) aryl, or C₆₋₁₄ (aryl) C₁₋₆alkyl;

D is hydrogen, C₁₋₁₀ alkyl, C₆₋₁₄ aryl, C₆₋₁₄ aryl(C₁₋₆ alkyl), (C₆₋₁₄ aryl)carbonyl, or (C₁₋₁₀ alkyl)carbonyl;

R₂ is hydrogen or lower alkyl,

(ii) or wherein

R (of formula II under (a)) and R₁ together with the chain to which they are attached from a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and

R₃ and R₂ have meaning as defined under (i);

(iii) or wherein

R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from lowercycloalkane which is unsubstituted or substituted by lower alkyl, oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and

R₃ and R meaning as defined under (i);

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or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

3. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament, for use in combination with

a) radiotherapy, or

b) heat shock and cytotoxic therapy for the treatment of tumors.

4. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) in combination with

a) radiotherapy, or

b) heat shock and cytotoxic therapy for the treatment of tumors.

5. A package comprising a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for use in combination with

a) radiotherapy, or

b) heat shock and cytotoxic therapy in the treatment of tumor.

6. A method according to claim 1, in which the matrix metalloproteinase inhibitor is a compound on formula I as defined in claim 2, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

7. A method according to claim 1, in which the matrix metalloproteinase inhibitor is one of the compounds disclosed in published international patent applications Nos. WO 98/14424, WO 97/22587 and EP 606046, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

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8. A method according to claim 1, in which the matrix metalloproteinase inhibitor is N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl) amino] -3-methyl -butaneamide hydrochloride) monohydrate, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.
9. A method according to claim 1 in which the matrix metalloproteinase inhibitor, or a pharmacologically acceptable salt or prodrug ester, is in the form of a enteral composition.
10. A method of treating cancer in a subject in need of such treatment which comprises radiotherapy in combination with heat shock therapy, and further comprises administering to the subject an effective amount of a matrix metalloproteinase.